

531 Rec'd PCT/PTO 15 JAN 2002

FORM PTO-1590 (REV. 3-90)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEYS DOCKET NO. 10/031501 16-080	
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)					
INTERNATIONAL APPLICATION NO. PCT/GB00/02584		INTERNATIONAL FILING DATE 5 July 2000 (05.07.2000)		PRIORITY DATE CLAIMED 16 July 1999 (16.07.1999)	
TITLE OF INVENTION METHOD OF PRODUCING SURGICAL GRADE CALCIUM SULPHATE					
APPLICANT(S) FOR DO/EO/US John Joseph Cooper					
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items under 35 U.S.C. 371: 1. ■ This express request to immediately begin national examination procedures (35 U.S.C. 371(f)). 2. ■ The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees as follows:					
CLAIMS	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
	TOTAL CLAIMS	46 - 20 =	26	x \$18.00	= \$468.00
	INDEPENDENT CLAIMS	1 - 3 =	0	x \$84.00	= \$0
MULTIPLE DEPENDENT CLAIMS(S) (if applicable)				+ \$270.00	
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(4)):					
<input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482)				690.00	\$740.00
<input type="checkbox"/> No International preliminary examination fee paid to USPTO (37 CFR 1.482) but International search fee paid to USPTO (37 CFR 1.445 (a)(2))					\$710.00
■ Neither International preliminary examination fee (37 CFR 1.482) nor International search fee (37 CFR 1.445(a)(2)) paid to USPTO.					\$1040.00
<input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provision of PCT Article 33(2) to 4)				\$100.00	
<input type="checkbox"/> International search fee prepared by EPO (37 CFR 1.492(a)(5))				\$890.00	\$1,040.00
Surcharge of \$130.00 for furnishing the National fee or oath or declaration later than 20 □ 30 mos. from the earliest claimed priority date (37 CFR 1.492(e)).					\$
TOTAL OF ABOVE CALCULATIONS					= \$1,508.00
Reduction by 1/2 for filing by small entity, if applicable. Applicant qualifies as a small entity under 37 C.F.R. § 1.27.					\$754.00
SUBTOTAL					= \$754.00
Processing fee of \$130.00 for furnishing the English translation later than 20 □ 30 mos. from the earliest claimed priority date (37 CFR 1.492(f)).					
TOTAL NATIONAL FEE					\$ 754.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)) \$40.00					\$ 40.00
TOTAL FEES ENCLOSED					\$794.00
a. ■ A check in the amount of \$794.00 to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$_____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-0630.					

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ATTORNEY'S DOCKET NUMBER
16-080

3. A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
 b. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
 c. ☐ has been transmitted by the International Bureau.
4. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
5. Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 b. ☒ have been transmitted by the International Bureau.
6. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
7. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)) is enclosed.
8. ☐ A translation of the Annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Other document(s) or information included:

9. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
10. ☒ An assignment document for recording.
 Please mail the recorded assignment document to:
 a. ☒ the person whose signature, name & address appears at the bottom of this page.
 b. ☐ the following:
11. The above checked items are being transmitted:
 a. ☐ before the 18th month publication.
 b. ☐ after publication and the Article 20 communication but before 20 months from the priority date.
 c. ☐ after 20 months but before 22 months (surcharge and/or processing fee included)
 d. ☐ after 22 months (surcharge and/or processing fee included)
 Note: Petition to revive (37 CFR 1.137(a) or (b)) is necessary if 35 U.S.C. 371 requirements submitted after 22 months and no proper demand for International Preliminary Examination was made by 19 months from the earliest claimed priority date.
 e. ☒ by 30 months and a proper demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
 f. ☐ after 30 months but before 32 months and a proper demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date (surcharge and/or processing fee included.)
 g. ☐ after 32 months (surcharge and/or processing fee included).
 Note: Petition to revive (37 CFR 1.137(a) or (b)) is necessary if 35 U.S.C. 371 requirements submitted after 32 months and a proper demand for International Preliminary Examination was made by 19 months from the earliest claimed priority date.
12. At the time of transmittal, the time limit for amending claims under Article 19
 a. ☐ has expired
 b. ☒ has not yet expired.
13. ☐ Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on _____, namely:
14. ☒ Enclosed is an Amendment Before Office Action.
15. ☒ Applicant qualifies as a small entity under 37 C.F.R. §127.

 Michael A. Miller
 NAME

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 SIGNATURE
 P-50,732
 REGISTRATION NO.

10/031501
531 Rec'd PCT/PT 15 JAN 2002
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: John J. Cooper Filed: (filed concurrently with application)
Serial No.: not yet assigned Art Unit: not yet assigned
Docket No.: 16-080

Title: **METHOD OF PRODUCING SURGICAL GRADE CALCIUM SULPHATE**

Watts, Hoffman, Fisher & Heinke Co., L.P.A.
1100 Superior Ave., Suite 1750
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Assistant Commissioner of Patents
BOX PATENT APPLICATION
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Dear Sir:

Prior to the examination of the present application, please amend the application as follows:

In the Specification:

On page 1, after the title and before the first line of text of the specification, please insert the following paragraph:

The present application claims priority from PCT/GB00/02584 filed
July 5, 2000.

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U. S. Postal Service as Express Mail addressed to the
Assistant Commissioner for Patents, Washington, D.C. 20231
on 1/15/02
by J. Kenson

In the Claims:

The following claims have been amended:

3. (Amended) A method according to claim 1, characterised in that the subsequent di-hydrate is formed into pellets.

8. (Amended) A method according to claim 5, characterised in that the calcining is hydrothermal to form α calcium sulphate hemi-hydrate.

12. (Amended) A method according to claim 5, characterised in that the calcining is carried out in dry heat conditions.

15. (Amended) A method according to claim 8, characterised in that the calcining is carried out for a period of a half to six hours.

17. (Amended) A method according to claim 5, characterised in that following calcining, the calcium sulphate hemi-hydrate is ground to a powder.

19. (Amended) A method according to claim 1, characterised in that the initial calcium sulphate di-hydrate is formed by mixing soluble calcium and sulphate salts such that calcium sulphate precipitates out.

21. (Amended) A method according to claim 19, characterised in that the calcium salt is a chloride.

22. (Amended) A method according to claim 19, characterised in that the calcium salt is a nitrate.

23. (Amended) A method according to claim 19, characterised in that the sulphate is a sodium salt.

24. (Amended) A method according to claim 19, characterised in that the sulphate is a potassium salt.

25. (Amended) A method according to claim 19, characterised in that the sulphate is an ammonium salt.

26. (Amended) A method according to claim 19, characterised in that the calcium and sulphate salts are provided in a substantially equal molecular ratio.

27. (Amended) A method according to claim 1, characterised in that the initial calcium sulphate di-hydrate is formed from neutralising lime with sulphuric acid.

28. (Amended) A method according to claim 1, characterised in that the dehydration of the initial calcium sulphate di-hydrate takes place within a temperature range 110-350°C.

30. (Amended) A method according to claim 1, characterised in that the dehydration of the initial calcium sulphate di-hydrate takes place at a temperature above 350°C to form insoluble anhydrite.

32. (Amended) A method according to claim 1, characterised in that the dehydration of the initial calcium sulphate di-hydrate by the application of heat takes place in an open container.

33. (Amended) A method according to claim 1, characterised in that the dehydration of the initial calcium sulphate di-hydrate by the application of heat takes place in a closed container.

34. (Amended) A method according to claim 1, characterised in that the dehydration of the initial calcium sulphate di-hydrate by the application of heat takes place hydrothermally in the presence of steam.

35. (Amended) A method according to claim 1, characterised in that the rehydration of the calcium sulphate anhydrite takes place immediately following dehydration.

36. (Amended) A method according to claim 1, characterised in that the calcium sulphate anhydrite is fully immersed in water for rehydration.

37. (Amended) A method according to claim 1, characterised in that the calcium sulphate anhydrite is fully immersed in a dilute salt solution for rehydration.

40. (Amended) A method according to claim 37, characterised in that the concentration of the salt solution is less than 1%.

42. (Amended) A method according to claim 1, characterised in that finely powdered calcium sulphate di-hydrate is added to be present during rehydration such that the powdered calcium sulphate acts as crystal seeds.

44. (Amended) A method according to claim 28, characterised in that the rehydration takes less than five days.

45. (Amended) A method according to claim 1, characterised in that the subsequent calcium sulphate di-hydrate is dried following crystallisation.

46. (Amended) A method according to claim 8, characterised in that the subsequent calcium sulphate di-hydrate is held in a damp condition prior to calcining.

Please cancel claim 47 without prejudice or disclaimer.

REMARKS


Entry of the foregoing Preliminary Amendment prior to examination of this application is respectfully requested.

The present application claims priority from and is a U.S. national application of PCT/GB00/02584 filed July 5, 2000. Claims 3, 8, 12, 15, 17, 19, 21-28, 30, 32-37, 40, 42 and 44-46 have been amended. Claim 47 has been cancelled without prejudice or disclaimer. Claims 1-46 are now pending. The claims are amended to change the claim dependencies.

Attached hereto is a marked-up version of the changes made to the application by this Preliminary Amendment.

Respectfully submitted,

Date: 1/15/02



Michael A. Miller
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Facsimile No.: 216-241-8151

Attachment: Version with Markings to Show Changes Made

VERSION WITH MARKINGS TO SHOW CHANGES MADEIn the Claims:

A paragraph has been added after the title and before the first paragraph in the application. The purpose of this paragraph is to claim priority to the corresponding PCT application.

The following claims have been amended as follows:

3. (Amended) A method according to [claims 1 or 2] claim 1, characterised in that the subsequent di-hydrate is formed into pellets.
8. (Amended) A method according to [any of claims 5 to 7] claim 5, characterised in that the calcining is hydrothermal to form α calcium sulphate hemi-hydrate.
12. (Amended) A method according to [any of claims 5 to 7] claim 5, characterised in that the calcining is carried out in dry heat conditions.
15. (Amended) A method according to [any of claims 8 to 14] claim 8, characterised in that the calcining is carried out for a period of a half to six hours.
17. (Amended) A method according to [any of claims 5 to 15] claim 5, characterised in that following calcining, the calcium sulphate hemi-hydrate is ground to a powder.
19. (Amended) A method according to [any of the previous claims] claim 1, characterised in that the initial calcium sulphate di-hydrate is formed by mixing soluble calcium and sulphate salts such that calcium sulphate precipitates out.
21. (Amended) A method according to [claims 19 or 20] claim 19, characterised in that the calcium salt is a chloride.
22. (Amended) A method according to [claims 19 or 20] claim 19, characterised in that the calcium salt is a nitrate.

23. (Amended) A method according to [any of claims 19 to 22] claim 19, characterised in that the sulphate is a sodium salt.

24. (Amended) A method according to [any of claims 19 to 22] claim 19, characterised in that the sulphate is a potassium salt.

25. (Amended) A method according to [any of claims 19 to 22] claim 19, characterised in that the sulphate is [a] an ammonium salt.

26. (Amended) A method according to [any of claims 19 to 25] claim 19, characterised in that the calcium and sulphate salts are provided in a substantially equal molecular ratio.

27. (Amended) A method according to [any of claims 1 to 18] claim 1, characterised in that the initial calcium sulphate di-hydrate is formed from neutralising lime with sulphuric acid.

28. (Amended) A method according to [any of the previous claims] claim 1, characterised in that the dehydration of the initial calcium sulphate di-hydrate takes place within a temperature range 110-350°C.

30. (Amended) A method according to [any of claims 1 to 27] claim 1, characterised in that the dehydration of the initial calcium sulphate di-hydrate takes place at a temperature above 350°C to form insoluble anhydrite.

32. (Amended) A method according to [any of the preceding claims] claim 1, characterised in that the dehydration of the initial calcium sulphate di-hydrate by the application of heat takes place in an open container.

33. (Amended) A method according to [any of claims 1 to 31] claim 1, characterised in that the dehydration of the initial calcium sulphate di-hydrate by the application of heat takes place in a closed container.

34. (Amended) A method according to [any of the preceding claims] claim 1, characterised in that the dehydration of the initial calcium sulphate di-hydrate by the application of heat takes place hydrothermally in the presence of steam.

35. (Amended) A method according to [any of the preceding claims] claim 1, characterised in that the rehydration of the calcium sulphate anhydrite takes place immediately following dehydration.

36. (Amended) A method according to [any of the preceding claims] claim 1, characterised in that the calcium sulphate anhydrite is fully immersed in water for rehydration.

37. (Amended) A method according to [any of claims 1 to 35] claim 1, characterised in that the calcium sulphate anhydrite is fully immersed in a dilute salt solution for rehydration.

40. (Amended) A method according to [any of claims 37 to 39] claim 37, characterised in that the concentration of the salt solution is less than 1%.

42. (Amended) A method according to [any of the previous claims] claim 1, characterised in that finely powdered calcium sulphate di-hydrate is added to be present during rehydration such that the powdered calcium sulphate acts as crystal seeds.

44. (Amended) A method according to [claims 28 or 29, or any of claims 32 to 43 when dependent on claims 28 or 29] claim 28, characterised in that the rehydration takes less than five days.

45. (Amended) A method according to [any of the preceding claims] claim 1, characterised in that the subsequent calcium sulphate di-hydrate is dried following crystallisation.

46. (Amended) A method according to claim 8 [or any of claims 9 to 44 when dependent on claim 8], characterised in that the subsequent calcium sulphate di-hydrate is held in a damp condition prior to calcining.

Claim 47 has been cancelled without prejudice or disclaimer.

METHOD OF PRODUCING SURGICAL GRADE CALCIUM SULPHATE

This invention concerns a method of producing surgical grade calcium sulphate and particularly but not exclusively a method of producing a resorbable osteoconductive bone void filler material.

Plaster of paris (hemi-hydrate calcium sulphate) is known to be suitable for use as a filler for bone defects. This material provides a number of required characteristics and does not produce any significant undesirable reaction within a body. Traditionally plaster of paris is produced from naturally occurring gypsum. This often has associated undesirable impurities. For medical applications and particularly for implantation high purity materials are obviously needed. Whilst it is possible for calcium sulphate to be produced synthetically, conventional techniques produce a material which has a high surface area which thus has a high water demand and therefore produces a low strength material when set. Such set material has a high dissolution rate and too short a residence time when implanted.

Plaster of paris, or more accurately calcium sulphate, has two modes of use as a bone filler. The first is in the di-hydrate form, usually as pellets which can be placed in a bone void. The second is as a hemi-hydrate powder which can be made up with water into a paste, which paste is mouldable to a required shape. Such materials are usable in the fields of orthopaedic, dental and maxillofacial surgery. Hemi-hydrate calcium sulphate has two forms. The first α is produced by hydrothermal treatment of the di-hydrate. The second β is produced by dry heat calcination. This latter form tends to have a low density, a higher water demand and therefore a lower strength and a faster dissolution rate than the α form.

According to the present invention there is provided a method of producing surgical grade calcium sulphate, the method comprising forming an initial calcium sulphate di-hydrate from synthetic constituents; dehydrating the initial calcium sulphate di-hydrate to form calcium sulphate anhydrite; and

subsequently rehydrating the calcium sulphate anhydrite and allowing subsequent calcium sulphate di-hydrate to crystallise out.

The subsequent di-hydrate may be used as a solid material bone filler and may be formed into pellets. The crystallised subsequent calcium sulphate di-hydrate may be ground prior to forming into pellets.

Alternatively, the subsequent calcium sulphate di-hydrate may be calcined to form calcium sulphate hemi-hydrate, which material can be mixed with water or a salt solution to form a settable paste.

The calcining may be hydrothermal to form α calcium sulphate hemi-hydrate, and may be carried out in an autoclave. The calcining may be carried out at a pressure of 1-6 bar, and desirably 2-3 bar. The calcining is preferably carried out for a half to five hours, and desirably one to two hours.

Alternatively, the calcining may be carried out in dry heat conditions. The calcining may be carried out at a temperature of 70 - 200°C and desirably at 150 - 175°C, and for a period of a half to six hours and desirably one to two hours.

Following calcining, the calcium sulphate hemi-hydrate is preferably ground to a powder, and desirably with a particle size of less than 150 microns.

The initial calcium sulphate di-hydrate may be formed by mixing soluble calcium and sulphate salts such that calcium sulphate precipitates out. The di-hydrate thus formed may be washed, and subsequently filtered, crushed and/or dried.

The calcium salt may be a chloride or nitrate. The sulphate may be a sodium, potassium or ammonium salt. The calcium and sulphate salts are preferably provided in a substantially equal molecular ratio.

Alternatively the initial calcium sulphate di-hydrate may be formed from neutralising lime with sulphuric acid.

The dehydration of the initial calcium sulphate di-hydrate preferably takes place within a temperature range 110 - 350° and desirably at less than 300°C, to form soluble calcium sulphate anhydrite. Alternatively the dehydration may take place at a temperature above 350°C to form insoluble anhydrite.

The dehydration of the initial calcium sulphate di-hydrate by the application of heat may take place in an open container, or in a closed container, or hydrothermally in the presence of steam.

The rehydration of the calcium sulphate anhydrite preferably takes place immediately following dehydration. The calcium sulphate anhydrite is preferably fully immersed in water or an aqueous solution for rehydration.

The rehydration may take place in water or a dilute salt solution. The salt solution may comprise succinic acid or a potassium sulphate solution, with a concentration of less than 1% and desirably substantially 0.1%.

Finely powdered calcium sulphate di-hydrate may be added to be present during rehydration such that the powdered calcium sulphate acts as crystal seeds, and the addition may be in the order of 5g per litre of water. For soluble anhydrite the rehydration preferably takes less than five days, and for insoluble anhydrite preferably more than five days.

The subsequent calcium sulphate di-hydrate is preferably dried following crystallisation. Alternatively, if it is to be autoclaved to form α hemi-hydrate it may be held in a damp condition.

Examples of the present invention will now be described by way of example only.

Example 1

4 moles of analytical grade potassium sulphate were dissolved in 2 l of deionised water. The resulting solution was added to a solution of 4 moles calcium nitrate in 2 l of deionised water. The precipitate so formed was washed free of all nitrate and filtered on a Buchner Funnel followed by a further wash on filter with 100ml of deionised water. The resultant filter cake was dried at 40°C. Its BET SSA (specific surface area measurement) was determined as 0.61 m²/gm.

500 gms of this calcium sulphate di-hydrate filter cake were lightly crushed, put into a 2 l borosilicate glass beaker, and placed in an oven at 200°C for 24 hours. On removal from the oven, 500 mls of deionised water - were added immediately to the beaker ensuring that all of the powder was immersed. This was allowed to soak for a period of 3 days, and then all supernatant liquid was drained away.

The resulting di-hydrate had a BET SSA of 0.06m²/gm. This coarse textured, granular, recrystallised di-hydrate was now placed in a stainless steel tray and autoclaved at 2.5 bar for a period of 2 hours. The α hemi-hydrate so formed was dried at 110°C for half hour prior to crushing in a pestle and mortar to pass a 150 micron mesh sieve.

The material so formed could be blended with 0.35 parts of water to form an easily workable and mouldable paste which became firm after 6 minutes and set to a hard, dense mass soon after.

This material blended with 0.35 parts of a 0.5% potassium sulphate solution formed an easily workable and mouldable paste which became firm after 3 minutes, and set to a hard dense mass soon after.

Example 2

2 moles of analytical grade calcium carbonate was added slowly and with gentle agitation to 2L of 1N analytical grade sulphuric acid in a 3 litre glass beaker. When the effervescence has subsided and the pH of the resulting suspension was substantially neutral, $\text{pH} = 7.0$, the suspended mass in its container was heated in an autoclave to a temperature of 130°C and maintained at that temperature for 3 hours. After cooling, the precipitated calcium sulphate was allowed to soak in the supernatant for a period of 3 days and then all supernatant liquid was drained away. This powder was treated hydrothermally as in Example 1 above to produce an α hemi-hydrate.

Example 3

500 gms of the precipitated calcium sulphate di-hydrate from Example 1 were put into a glass beaker, which was placed in an oven at 200°C for 24 hours. On removal from the oven, 500 mls of 0.1% succinic acid solution were added to the beaker, ensuring that all of the powder was immersed. This was soaked for 16 hours, at which time the supernatant liquid was drained away to reveal a coarse textured recrystallised gypsum powder.

This powder was treated hydrothermally as in Example 1 above, followed by drying and crushing.

The resulting α hemi-hydrate was blended with 0.45 parts of water to form a paste which became firm after 6 minutes and set to a hard, dense mass soon after.

Example 4

500 gms of the precipitated calcium sulphate di-hydrate from Example 2 were calcined in an oven at 400°C for 2 hours. The anhydrite so formed was the orthorhombic or so called dead burned variety. This was removed from the oven, immersed in deionised water and allowed to soak for a period of 14 days. The supernatant liquid was drained away to reveal a coarse, gritty recrystallised

gypsum powder. This was hydrothermally treated in an autoclave for 2½ hours at 1.7 bar. The resulting α hemi-hydrate was dried at 110°C and crushed to pass a 125 micron mesh sieve. This gave a material which was blended with 0.38 parts of sterile, deionised water to form a mouldable paste which became firm 5 minutes after mixing, and set to a hard mass soon after.

Example 5

Recrystallised di-hydrate prepared according to Example 1 was dried at 40°C overnight. The dried material was crushed to pass a 150 micron mesh sieve and the resulting fine powder was heated in a shallow stainless steel tray at a depth of 2 cm for 2 hours at 165°C. The hemi-hydrate so formed was of the β variety, and was blended with 0.65 parts of sterile deionised water to form a mouldable paste which set to give a firm mass.

Example 6

500gms of the precipitated calcium sulphate di-hydrate from Example 1 were put into a glass beaker, which was placed in an oven at 150°C for 40 minutes. On removal from the oven, the resultant β hemi-hydrate was added to 600ml of deionised water and mixed to form a fluid mass. This was poured into a shallow stainless steel tray and allowed to re-hydrate and set. The following day the set gypsum in the stainless steel tray was put into an oven at 250°C for 20 hours to allow for complete dehydration. The resulting calcium sulphate anhydrite was covered with deionised water and allowed to soak for a period of 4 days and then all supernatant liquid was drained away to reveal a coarse textured recrystallised gypsum powder. This powder was treated hydrothermally as in Example 1 above to produce an α hemi-hydrate.

Summary

Examples 1 and 2 show alternative means of precipitating and subsequently dehydrating the initial calcium sulphate di-hydrate.

Example 4 shows that the insoluble anhydrite requires a much longer crystallisation time than the soluble variety. Example 5 shows the use of dry heat calcination to produce the β hemi-hydrate. It has been found that using a salt for the rehydration speeds up the process, as is illustrated in Example 3. Finely powdered gypsum may be added to act as crystal seeds.

Example 6 shows that the synthetic precipitated calcium sulphate dihydrate can first be formed into a hemi-hydrate followed by re-hydration with a minimum quantity of water to form a set mass of di-hydrate. This set dihydrate can then be dehydrated and recrystallised as previously described.

The above examples describe production of calcium sulphate hemi-hydrate which can be formed into a paste. The α hemi-hydrate thus formed can be blended with 0.30 to 0.40 parts water or saline solution to give a mouldable paste which sets to a firm mass. The β hemi-hydrate requires 0.55 to 0.70 parts water to form an appropriate paste.

If the calcium sulphate is required to be used in a pellet form, the calcination from the di-hydrate to the hemi-hydrate is not required. The subsequent di-hydrate would be ground or crushed and formed into pellets of an appropriate size.

There is thus described a method of producing surgical grade calcium sulphate which combines the advantages of the synthetic route with the characteristics encountered with naturally occurring gypsum. The method is relatively straightforward and can thus be readily reproduced, and without significant extra costs. The calcium sulphate produced by the methods herein described can provide an improved delivery means for the controlled release of medicaments into the body by virtue of their high chemical and phase purity compared to naturally occurring calcium sulphate. This provides for a more consistent and predictable rate of dissolution of the calcium sulphate and release of the medicament contained therein.

Various modifications may be made without departing from the scope of the invention. For example, the initial di-hydrate may be formed by neutralising lime with sulphuric acid. Other materials such as calcium chloride or sodium sulphate, may be used to form the initial calcium sulphate. Other salts may be used during the process as is required. Other conditions may be applicable to the dehydration, rehydration or calcining.

Whilst endeavouring in the foregoing specification to draw attention to those features of the invention believed to be of particular importance it should be understood that the Applicant claims protection in respect of any patentable feature or combination of features hereinbefore referred to and/or shown in the drawings whether or not particular emphasis has been placed thereon.

Claims

1. A method of producing surgical grade calcium sulphate characterised in that the method comprises forming an initial calcium sulphate di-hydrate from synthetic constituents; dehydrating the initial calcium sulphate di-hydrate to form calcium sulphate anhydrite; and subsequently rehydrating the calcium sulphate anhydrite and allowing subsequent calcium sulphate di-hydrate to crystallise out.
2. A method according to claim 1, characterised in that the subsequent di-hydrate is used as a solid material bone filler.
3. A method according to claims 1 or 2, characterised in that the subsequent di-hydrate is formed into pellets.
4. A method according to claim 3, characterised in that the crystallised subsequent calcium sulphate di-hydrate is ground prior to forming into pellets.
5. A method according to claim 1, characterised in that the subsequent calcium sulphate di-hydrate is calcined to form calcium sulphate hemi-hydrate.
6. A method according to claim 5, characterised in that the calcium sulphate hemi-hydrate is mixed with water to form a settable paste.
7. A method according to claim 5, characterised in that the calcium sulphate hemi-hydrate is mixed with a salt solution to form a settable paste.
8. A method according to any of claims 5 to 7, characterised in that the calcining is hydrothermal to form α calcium sulphate hemi-hydrate.
9. A method according to claim 8, characterised in that the calcining is carried out in an autoclave.

10. A method according to claim 9, characterised in that the calcining is carried out at a pressure of 1-6 bar.
11. A method according to claim 10, characterised in that the calcining is carried out at 2-3 bar.
12. A method according to any of claims 5 to 7, characterised in that the calcining is carried out in dry heat conditions.
13. A method according to claim 12, characterised in that the calcining is carried out at a temperature of 70 - 200°C.
14. A method according to claim 13, characterised in that the calcining is carried out at 150 - 175°C.
15. A method according to any of claims 8 to 14, characterised in that the calcining is carried out for a period of a half to six hours.
16. A method according to claim 15, characterised in that the calcining is carried out for one to two hours.
17. A method according to any of claims 5 to 15, characterised in that following calcining, the calcium sulphate hemi-hydrate is ground to a powder.
18. A method according to claim 17, characterised in that the powder has particle size of less than 150 microns.
19. A method according to any of the previous claims, characterised in that the initial calcium sulphate di-hydrate is formed by mixing soluble calcium and sulphate salts such that calcium sulphate precipitates out.
20. A method according to claim 19, characterised in that the initial di-hydrate thus formed is washed, and subsequently filtered, crushed and/or

dried.

21. A method according to claims 19 or 20, characterised in that the calcium salt is a chloride.
22. A method according to claims 19 or 20, characterised in that the calcium salt is a nitrate.
23. A method according to any of claims 19 to 22, characterised in that the sulphate is a sodium salt.
24. A method according to any of claims 19 to 22, characterised in that the sulphate is a potassium salt.
25. A method according to any of claims 19 to 22, characterised in that the sulphate is an ammonium salt.
26. A method according to any of claims 19 to 25, characterised in that the calcium and sulphate salts are provided in a substantially equal molecular ratio.
27. A method according to any of claims 1 to 18, characterised in that the initial calcium sulphate di-hydrate is formed from neutralising lime with sulphuric acid.
28. A method according to any of the previous claims, characterised in that the dehydration of the initial calcium sulphate di-hydrate takes place within a temperature range 110 - 350°C.
29. A method according to claim 28, characterised in that the dehydration of the initial calcium sulphate di-hydrate takes place at less than 300°C.
30. A method according to any of claims 1 to 27, characterised in that the dehydration of the initial calcium sulphate di-hydrate takes place at a

temperature above 350°C to form insoluble anhydrite.

31. A method according to claim 30, characterised in that the rehydration takes more than five days.
32. A method according to any of the preceding claims, characterised in that the dehydration of the initial calcium sulphate di-hydrate by the application of heat takes place in an open container.
33. A method according to any of claims 1 to 31, characterised in that the dehydration of the initial calcium sulphate di-hydrate by the application of heat takes place in a closed container.
34. A method according to any of the preceding claims, characterised in that the dehydration of the initial calcium sulphate di-hydrate by the application of heat takes place hydrothermally in the presence of steam.
35. A method according to any of the preceding claims, characterised in that the rehydration of the calcium sulphate anhydrite takes place immediately following dehydration.
36. A method according to any of the preceding claims, characterised in that the calcium sulphate anhydrite is fully immersed in water for rehydration.
37. A method according to any of claims 1 to 35, characterised in that the calcium sulphate anhydrite is fully immersed in a dilute salt solution for rehydration.
38. A method according to claim 37, characterised in that the salt solution comprises succinic acid.
39. A method according to claim 37, characterised in that the salt solution comprises potassium sulphate solution.

40. A method according to any of claims 37 to 39, characterised in that the concentration of the salt solution is less than 1%.

41. A method according to claim 40, characterised in that the concentration of the salt solution is substantially 0.1%.

42. A method according to any of the previous claims, characterised in that finely powdered calcium sulphate di-hydrate is added to be present during rehydration such that the powdered calcium sulphate acts as crystal seeds.

43. A method according to claim 42, characterised in that addition is in the order of 5g per litre of water.

44. A method according to claims 28 or 29, or any of claims 32 to 43 when dependent on claims 28 or 29, characterised in that the rehydration takes less than five days.

45. A method according to any of the preceding claims, characterised in that the subsequent calcium sulphate di-hydrate is dried following crystallisation.

46. A method according to claim 8, or any of claims 9 to 44 when dependent on claim 8, characterised in that the subsequent calcium sulphate di-hydrate is held in a damp condition prior to calcining.

47. Any novel subject matter or combination including novel subject matter disclosed herein, whether or not within the scope of or relating to the same invention as any of the preceding claims.

PATENT
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: John J. Cooper

Serial No.: N/A Group No.: N/A

Filed: Herewith

Title: Method of Producing Surgical Grade Calcium Sulphate

Examiner: N/A

Claims Priority of: PCT/GB00/02584

Assistant Commissioner for Patents
BOX DO/EO/US
Washington, D.C. 20231


ASSOCIATE POWER OF ATTORNEY

The undersigned, duly appointed attorney in the matter of the above-identified application hereby appoints Michael A. Miller, Reg. No. P 50,732, associate attorney with full power in the premises to prosecute this application, to make alterations and amendments therein, to sign the drawings, to receive the patent, and to transact all business in the U.S. Patent & Trademark Office connected therewith.

Please charge deposit account no. 23-0630 for any fees in connection with this.

Respectfully submitted,

Date: January 15, 2002


Thomas E. Fisher
Reg. No. 18,271
Attorney of Record

Express Mail Label No. ELE609731B1US

I hereby certify that this paper is being deposited with the U. S. Postal Service as Express Mail addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

on 1/15/02

By: [Signature]

Declaration and Power of Attorney for Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Improvements in Relation to a Method of Producing Surgical Grade Calcium Sulphate

the specification of which:

- () is attached hereto.
- () was filed on
as Application serial no.
and was amended on
- (X) was described and claimed in PCT International Application No.
PCT/GB00/02584, filed on 5th July 2000 and amended under PCT
Article 19 on

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

If this application is a continuation-in-part application, I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56, which became available between the filing date of the prior application and the national or PCT international filing date of this continuation-in-part application.

I hereby claim foreign priority under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

<u>Number</u>	<u>Country</u>	<u>Filing Date</u>	<u>Priority Claimed</u> (Yes/No)
9916601.9	United Kingdom	16th July 1999	YES

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

<u>Application No.</u>	<u>Filing Date</u>
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I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below, and insofar as the subject matter of each of the claims of

this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing of this application:

Application Serial No. Filing Date Status - Patented, Pending, Abandoned

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: T.E. Fisher, Reg. No. 18,271; L.L. Heinke, Reg. No. 19,471; J.G. Watterson, Reg. No. 20,180; L.J. Raney, Reg. No. 23,078; J.R. Hlavka, Reg. No. 29,076; S.J. Schultz, Reg. No. 29,108; R.A. Sharpe, Reg. No. 34,722; G.L. Pinchak, Reg. No. 37,697; P.A. Serbinowski, Reg. No. 34,429; J. Nock-Hinton, W.A. Johnston and K.J. Smith. Send correspondence to:

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